Baghdad Journal of Biochemistry and Applied Biological Sciences
2025; 6, 3: 127-138, e-ISSN: 2706-9915, p-ISSN: 2706-9907

NARRATIVE REVIEW

DNA Damage prevention by the use of computationally designed Microplastics adsorbing Chemicals

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Article's Information

Received: 02.06.2025
Accepted: 26.06.2025
Published: 10.07.2025

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Pages:127-138

https://doi.org/10.47419/bjbabs.v6i03.406

Abstract

Background: Cancer development is driven by uncontrolled cellular proliferation resulting from the accumulation of genetic mutations. One of the most well-studied mechanisms behind these mutations is DNA damage. Cellular DNA is under constant threat of damage by exogenous and endogenous sources. Microplastics are one of these exogenous sources and characterized by their small size and high surface-area-to-volume ratio, have the ability to interact strongly with biological systems, leading to cytotoxicity, cell damage, and DNA mutations that increase cancer risk. Microplastics uptake and subsequent bioaccumulation in the human body are increasingly considered to negatively impact the body's usual mechanisms of damage repair, with resultant increases in apoptosis, necrosis, inflammation, oxidative stress, and aberrant immune responses.

Objective: Design a compound for the efficient absorption of microplastics by the use of PubChem, Avogadro, PyMOL, and SWISSADME.

Methods: A general approach to designing such a compound include: 1. Targeting and Binding Microplastics. 2. Biocompatibility. 3. Efficient Elimination. 4. Delivery Mechanism.

Results: We found that modified chitosan could be the best compounds for microplastics adsorption from human body. PubChem was used to obtain the Chitosan chemical structure ($C_{56}H_{103}N_9O_{39}$) M.wt: 1526.5 g/mol. Avogadro was used for Chitosan fragmentation in to smaller pieces to increase solubility, permeability through cellular membrane and enhance activity. PyMOL was used to check out the 3D structure and its functional groups. SWISSADME was applied to analyze GI absorption, skin permeation, bioavailability, and the level of compliance with Lipinski rules of 5.

Conclusion: This research highlights the potential of chitosan-based compounds as a prevention strategy for mitigating microplastic-induced carcinogenesis.

Keywords: Avogadro, DNA damage, Microplastics, Modified chitosan, SWISSADME.

1.Introduction

Cellular DNA is continuously at risk of damage from both external and internal sources. External factors like ionizing radiation (IR) and certain chemotherapy drugs (e.g., platinum-based agents) can cause DNA double-strand breaks (DSBs), which are especially deadly to cancer cells. Internally, byproducts of cellular metabolism, such as aldehydes and reactive oxygen species, can create obstacles during DNA replication, potentially leading to replication-associated DSBs or errors in chromosome separation during cell division, resulting in DNA breaks. The DNA damage response (DDR) is essential for genome stability, identifies DNA damage and activate a complex signaling network that temporarily stop the cell cycle and repair DNA damage [1,2,3].

DNA damage

In the normal healthy cells, The DDR plays a vital role via extrinsic and intrinsic mechanisms to prevent cancer development. Firstly; prevention of genetic errors accumulation which may lead to malignancy transformations. Secondly; activation of regulated cell death program when the DNA damages could not be repaired. Finally; specific DDR components regulate the recruitment of activated immune cells to remove the potentially oncogenic cells [4,5]. Exposure to environmental chemicals during embryonic and fetal periods can increase the risk of adverse health outcomes or disorders later in life as well as disrupt normal developmental processes [6,7]. Exposure to neurotoxic chemicals and stress during maternal prenatal period may increase the neurological disorders in later life stages [8]. The epigenome is particularly susceptible to environmental influences during prenatal development, as this phase involves significant epigenetic reprogramming and programming. These processes are essential for establishing cell- and tissue-specific gene expression patterns [9,10,11].

Plastic pollution; Plastic was first synthesized in the early 20th century and became widely available after World War II. Since then, plastic pollution has elevated dramatically, with global production reportedly surging from 2.3 million tons in 1950 to 348 million tons in 2017 [12]. The issue of plastic pollution was first identified in the oceans during the 1970s through studies on plankton. Today, it is estimated that approximately 3.2 million tons of primary microplastics (MPs) are released into the environment annually. This trend shows no signs of slowing down in the near future, making plastic pollution a major environmental challenge. Plastic debris, defined as plastic items found in natural environments without serving their intended purpose, is persistent, mobile, and ubiquitous across both terrestrial and aquatic ecosystems. With the rise of industrialization and globalization, plastics have become integral to various industries and daily life. Over time, these materials break down into smaller fragments or particles through physical, chemical, and biological processes. Microplastics, which are plastic particles smaller than 5 mm, are categorized into two types: primary MPs, which are intentionally manufactured at this size for commercial use (e.g., plastic pellets, synthetic textiles, and microbeads), and secondary MPs, which result from the environmental degradation of larger plastic items like bottles, bags, and packaging. Regardless of their origin, the ingestion and bioaccumulation of microplastics in the human body are increasingly linked to adverse health effects. These include disruptions to the body's natural damage repair mechanisms, leading to increased apoptosis (programmed cell death), necrosis (cell death due to injury), inflammation, oxidative stress, and abnormal immune responses. The growing presence of microplastics in the environment poses a significant threat to both ecosystems and human health [13,14].

Exposure to microplastics:

The ingestion of MPs by humans starts at an early age and continues throughout life. While adults are estimated to consume between 0.1 to 5 grams of MPs per week, young children face significantly higher exposure. Research has revealed that infants using plastic feeding bottles ingest an average of 1,580,000 microplastic particles each day [15]. This level of exposure is roughly 2,600 times higher than the combined intake of microplastics from water, food, and air in adults. These findings underscore the increased susceptibility of young children to microplastic contamination [16]. Certain studies have examined the expression of genes related to oxidative stress and the nervous system to assess whether the observed rise in locomotive activity is connected to alterations in these genes. These studies indicate that exposure to microplastics (MPs) increases reactive oxygen species (ROS) levels, prompting the activation of the cellular antioxidant defense system to moderate oxidative stress [17]. and increase the risk of hypertension and hypertension-associated cardiovascular injury [18]. A study examining DNA methylation in zebrafish during their later life stages explored the behavioral deficits caused by early-life exposure to polystyrene microplastics (PS-MPs). Through the analysis of molecular markers, including gene expression and DNA methylation patterns, the research demonstrated that PS-MPs can alter DNA methylation and induce neurodevelopmental toxicity. These results underscore the potential long-term consequences of microplastic exposure on neurological health and development [19]. Another study suggested that MPs may disrupt the integrity of the colonic mucus layer, impairing its protective role. This interaction among MPs, gut microbiota, and the mucus layer could contribute to the development of colorectal cancer (CRC). MPs tend to accumulate in the colon, potentially elevating the risk of colorectal carcinogenesis. However, more research is required to fully elucidate the role of MPs in CRC pathogenesis and their overall impact on gut health [20].

Microplastic composition: Plastics, though chemically inert, often contain additives that can leach into the environment, causing issues like inflammation. Their durability leads to environmental persistence and accumulation in the food chain. Additives can bind to microplastics, enabling them to transport harmful chemicals, thereby exacerbating their environmental and health impacts [21].

MPs and Carcinogenesis: Carcinogenesis can arise through either genotoxic or non-genotoxic approaches. Genotoxic carcinogenesis is driven by direct DNA damage inflicted by mutagens. MPs have the capacity to transport harmful chemicals absorbed from the environment, such as persistent organic pollutants, polycyclic aromatic hydrocarbons, and hydrophobic organic compounds. This ability stems from the chemical properties of MP surfaces, which enable them to adsorb hydrophobic substances, including some carcinogens, and interact with charged molecules, ions, and toxic metals through electrostatic forces [22,23]. This is attributed to the chemical characteristics of MP surfaces, which enable them to adsorb hydrophobic compounds (some are carcinogenic), interact with charged molecules and ions (toxic metals) through electrostatic interactions, and even facilitate the adhesion of pathogenic bacteria. Such MP-mediated exposures present substantial health risks, particularly through the direct transfer of toxic chemicals associated with MPs to the underlying epithelial tissues [24].

Plastic-related chemicals (Microplastics Component): Two primary classes of plastic-related chemicals present considerable risks to human health: bisphenols and phthalates. Bisphenols, are endocrine-disrupting compound with estrogenic properties, is commonly found in everyday items such as water bottles and food packaging. It interferes with hormonal functions, negatively affecting reproductive health, and may also influence the immune system, although research in this area is still limited and inconclusive. Phthalates, such as diethylhexyl phthalate (DEHP), are additives used in plastics, sometimes comprising up to 40-50% of products like medical devices. Both BPA and phthalates mimic natural hormones, binding to their receptors and disrupting gene expression, homeostasis, reproduction, and development. Mps, composed of polymer chains (carbon, hydrogen, oxygen), can release toxic chemicals like BPA (a key component of polycarbonate plastics) and phthalates when exposed to heat, stress, or repeated use. These chemicals, along with other additives, leach out over time, posing additional health risks. BPA becomes toxic when its bonds break down, while phthalates like DEHP are known to leach from plastics [25].

How Microplastic-induced cancer: Microplastics, characterized by their small size and high surface-area-to-volume ratio, have the ability to interact strongly with biological systems, leading to cytotoxicity, cell damage, and DNA mutations that increase cancer risk. When improperly disposed of in water, they absorb carcinogenic hydrophobic pollutants, further contributing to DNA damage. Additionally, heavy metals like arsenic, cadmium, chromium, mercury, and lead, used in plastic production and classified as carcinogens by the International Agency for Research on Cancer, enhance the carcinogenic potential of microplastics, posing significant health risks [26]. Epidemiological studies have demonstrated a significant association between chronic exposure to microplastics and the onset of cancer in both humans and animals. Because of their tiny size, microplastics are ingested by various marine organisms, eventually infiltrating the human food chain through bioaccumulation [27].

Once ingested, microplastics smaller than 2.5 mm can enter the digestive tract through endocytosis, a cellular process facilitated by microfold cells in Peyer’s patches. The cumulative effect of microplastic exposure depends on factors like hydrophobicity and chemical composition. This hypothesis is supported by the detection of microplastics in human stool samples, providing direct evidence of plastic ingestion. Such findings underscore the potential link between microplastic consumption and the development of various cancers [28].

Cancer: Significantly, both types of compounds can also trigger epigenetic changes when exposure occurs during critical developmental periods. This leads us to explore their role in predisposing individuals to certain types of cancer. For instance, perinatal exposure to BPA has been linked to an increased risk of breast cancer [29]. However, the molecular mechanisms underlying this process remain unclear. To better understand how this modulation occurs, another research group conducted experiments using mice, specifically examining the effects of in-utero exposure to this compound [30].BPA influenced the protein expression of key targets in the ER pathway, including cyclin D1, c-myc, and Bcl-2. Additionally, it triggered the simultaneous activation of erbB2, EGFR, erbB-3, Erk1/2, and Akt, along with the upregulation of their associated growth factors and ligands [31]. Breast tissue proliferation is regulated by estrogen receptors (ERs) and their natural ligands, which are present at higher levels in females than in males. Exposure to BPA appears to induce epigenetic reprogramming with long-term effects across various cell types. Notably, perinatal exposure to BPA not only increases the risk of mammary neoplasia but also predisposes offspring to cancer development, even after a single exposure to a potent carcinogen like 7,12-dimethylbenz(a)anthracene (DMBA). Exposure to phthalates during critical developmental periods, similar to bisphenols, has been linked to sexual dysfunction in both males and females, as well as the progression of breast cancer. These pro-tumoral effects of phthalates are primarily attributed to their interactions with estrogen receptors (ERs) rather than epigenetic modifications. Specifically, perinatal exposure to DEHP, a common phthalate, has not been associated with epigenetic alterations in genes related to breast cancer, underscoring the role of ER-mediated mechanisms in its carcinogenic effects [32,33,34].

Cancer causing mechanism: Additionally, 30 nm polystyrene nanoparticles were observed to form large vesicle-like structures within the endocytic pathway in macrophages and human cancer cell lines, including A549, HepG-2, and HCT116. These nanoparticles disrupted vesicle transport and interfered with the distribution of proteins essential for cytokinesis, leading to the formation of binucleated cells. Moreover, acute oral exposure to positively charged polystyrene nanoparticles was found to potentially impair intestinal iron transport and cellular uptake mechanisms [35].

Prata et al. (2020) demonstrated that the ingestion of microplastics could trigger chronic inflammation and irritation, potentially causing DNA damage. Earlier studies also indicated that the release of pro-inflammatory mediators, which promote angiogenesis, contributes to the development and progression of malignancies [36]. The presence of polycyclic aromatic hydrocarbons in food and water has emerged as a widespread concern [37].

A study by Sharma et al. (2022) revealed that microplastics can adsorb up to 236 μg/L of polycyclic aromatic hydrocarbons from water, with their leaching being 1,000 times more hazardous than benzopyrene, a known carcinogen [28]. Primarily ingested through the stomach, microplastics significantly increase cancer risk, though their specific effects on the stomach remain poorly understood despite extensive research on their broader human health impacts [25]. A 2022 study by Kim et al. revealed that prolonged microplastic exposure raises stomach cancer risk by increasing asialoglycoprotein receptor 2 (ASGR2) expression. Elevated ASGR2 levels are tied to cancer hallmarks like CD44, N-cadherin, PD-L1, and enhanced cell proliferation. Excessive exposure also correlated with lower survival rates and faster tumor growth [38].

Wang et al. (2023) found that microplastic toxicity to human colorectal adenocarcinoma cells depends on size, with 0.3 mm, 0.5 mm, and 6 mm particles showing high toxicity, while 1 mm and 3 mm particles were less toxic. Smaller microplastics had a higher uptake rate (73%) than larger ones (30%), linking increased surface area to greater oxidative stress [39].

Chitosan: Chitosan, also known as poliglusam, is a linear polysaccharide composed of β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine units. Naturally occurring chitosan is found in the cell walls of fungi, as well as in soil and sediments, where it is generated through the enzymatic degradation of chitin by specific bacterial groups that produce chitin deacetylase or chitosanase enzymes. In contrast, commercially available chitosan is typically derived from the chemical deacetylation of chitin extracted from the exoskeletons of marine crustaceans, such as shrimp. We used Pubchem to find out the chemical structure of Chitosan and the number of its atoms; Chemical Safety: Laboratory Chemical Safety Summary (LCSS) Datasheet. Molecular Formula: $C_{56}H_{103}N_9O_{39}$. Molecular Weight: 1526.5 g/mol. Computed by PubChem 2.2 (PubChem release 2021.10.14) [40].

2. Materials and Methods

Designing a compound for the efficient absorption of microplastics from the human body is a complex but important challenge. A general approach to designing such a compound:

2-1. Targeting and Binding Microplastics

The compound should possess the ability to selectively attach to microplastics. Key considerations include:

- Surface Chemistry of Microplastics: Microplastics are hydrophobic (water-repellent), suggesting that a compound with hydrophobic or amphiphilic (containing both hydrophilic and hydrophobic properties) characteristics could effectively interact with them.
- Electrostatic Interactions: Microplastics often have a slight negative charge. Incorporating a cationic (positively charged) compound could improve binding through electrostatic attraction.
- Functional Groups: The inclusion of functional groups such as carboxyl, hydroxyl, or amine groups may facilitate interactions with the surface of microplastics.

2-2. Biocompatibility

The compound must be non-toxic and biocompatible to ensure safety for human use. Potential classes of compounds to explore include:

- Biodegradable Polymers: Biopolymers such as chitosan (derived from chitin) are both biocompatible and capable of interacting with plastic particles through hydrophobic interactions.

- Cyclodextrins: These cyclic oligosaccharides are known for forming host-guest complexes and can be chemically modified to improve their interaction with microplastics.
- Natural Adsorbents: Materials like activated carbon or algae-based substances have demonstrated potential in absorbing contaminants, though they may require modifications to be suitable for human applications.

2-3. Efficient Elimination

The compound should be designed for easy removal from the body after binding to microplastics. Key considerations include:

- Excretion Pathways: The compound should be engineered to pass through the body and be excreted via urine or feces, avoiding absorption into tissues. Factors such as size and hydrophilicity are critical in achieving this.
- Enzyme-Responsive Linkers: Incorporating enzyme-responsive linkers can enable the compound to break down after fulfilling its function, facilitating safe and efficient excretion.

2-4. Delivery Mechanism

The delivery method is critical for effectively capturing microplastics in the digestive system or bloodstream:

- Oral Administration: If targeting microplastics in the digestive tract, the compound must be orally administered and designed to remain stable in the acidic environment of the stomach and in the presence of bile.
- Bloodstream Capture: For systemic microplastic capture, specific particles could be engineered to circulate in the bloodstream and bind to microplastics effectively.

Modified Chitosan Particles

We can begin with a core of modified chitosan particles, leveraging chitosan's established affinity for plastics and its biocompatibility. By introducing hydrophobic and cationic functional groups, we can enhance its binding capabilities, while incorporating enzyme-cleavable linkers would ensure safe and efficient excretion from the body.

Bioinformatics Tools:

1. **PubChem:** We retrieved the chemical structures and properties of the compounds from PubChem, a comprehensive database of small molecules and their biological activities.
2. **Avogadro:** Molecular modeling and optimization were performed using Avogadro, an open-source software for chemical structure visualization and geometry optimization.
3. **PyMOL:** Protein-ligand interactions and 3D structural visualizations were analyzed using PyMOL, a molecular graphics system for rendering and animating biomolecular structures.
4. **SwissADME:** Pharmacokinetic properties, including drug-likeness and bioavailability, were predicted using SwissADME, a web-based tool for evaluating absorption, distribution, metabolism, and excretion (ADME) parameters.

3. Results and Discussion

Results:

PubChem; we used this website to find out the chemical structure of Chitosan and the number of its atoms (Figure 1).

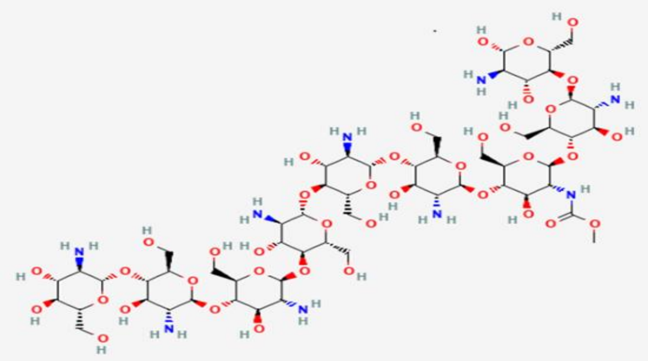

Figure 1: Chemical Structure of Chitosan, Molecular Formula: $C_{56}H_{103}N_9O_{39}$ obtained by PubChem.

DrugBank; Generic Name: Chitosan low molecular weight

DrugBank Accession Number: DB14155

Chitosan, also known as poliglusam, is a linear polysaccharide composed of β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine units.

Table 1: General characteristics of chitosan including the name, ID, Molecular Formula and Molecular Weight.

Small molecule	Chitosan
PubChem ID	71853
Molecular formula	$C_{56}H_{103}N_9O_{39}$
Molecular weight	1526. 5 g/mol

Chitosan is widely recognized as a rich source of dietary fiber and is utilized as a functional food ingredient or additive due to its diverse bioactive properties. It exhibits notable antimicrobial and antioxidant activities, along with the ability to influence protein aggregation, emulsification, film formation, clarification, and fatty acid absorption. These multifunctional characteristics make chitosan a valuable material in various industrial and biomedical applications [40,41].

However, chitosan's high molecular weight (1526.5 g/mol) and large molecular size pose significant challenges for its bioavailability, particularly in crossing biological barriers such as the blood-brain barrier (Table 1) To address this limitation, computational tools like Avogadro have been employed to model and facilitate the breakdown of chitosan into smaller, more bioavailable fragments, thereby enhancing its potential for therapeutic and functional applications.

Avogadro is an advanced molecule editor and visualizer designed for cross-platform use in computational chemistry, molecular modeling, bioinformatics, materials science, and related areas. It offers flexible high-quality rendering and a powerful plugin architecture (Figure 2).

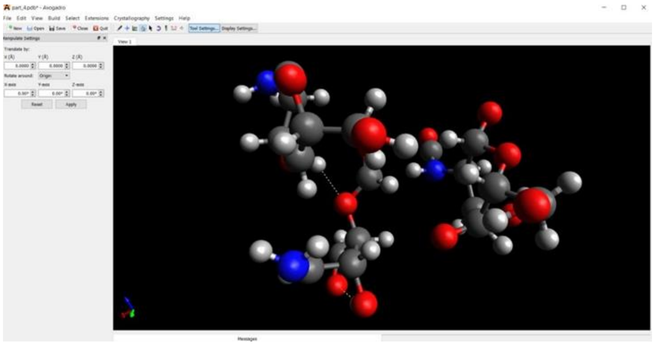

Figure 2: Avogadro was used to break down the Chitosan into 4 smaller parts. The figure represents the smaller part of fragmented chitosan.

After Chitosan fragmentation we used PyMOL for molecular visualization. PyMOL is a user-sponsored molecular visualization system on an open-source foundation, maintained and distributed by Schrödinger. It can produce high-quality 3D images of small molecules and biological macromolecules (Figure 3).

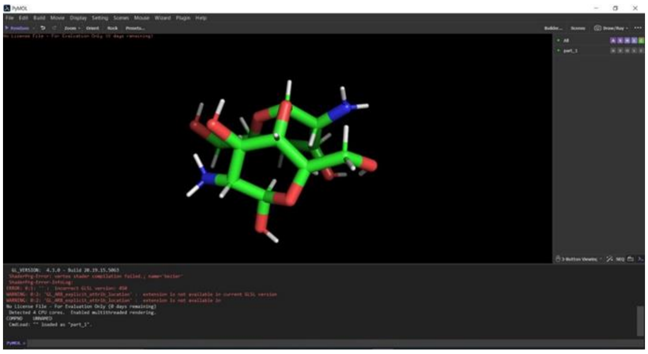

Figure 3: PyMOL was used for 3D visualization of fragmented Chitosan. Visualize ligand binding, interactions, highlight hydrogen bonds, salt bridges and hydrophobic pockets.

Biocompatibility

Using bioinformatics tools to assess the biocompatibility of chitosan for human use involves leveraging computational approaches to predict how the material might interact with biological systems, tissues, and cells. While traditional in vitro and in vivo testing is essential for definitive biocompatibility assessment, bioinformatics can provide valuable insights during the early stages of research or development. Here are some bioinformatics-based approaches to evaluate the biocompatibility of chitosan:

- **ADMET Profiling: Chemical absorption, distribution, metabolism, excretion, and toxicity.**

Chitosan, is a linear polysaccharide consisting of D-glucosamine. The SwissADME Web tool enables the computation of key physicochemical, pharmacokinetic, drug-like and related parameters for one or multiple molecules. This figure representing the structure of D-glucosamine as the main component of fragmented modified Chitosan by SwissADME (Figure 4).

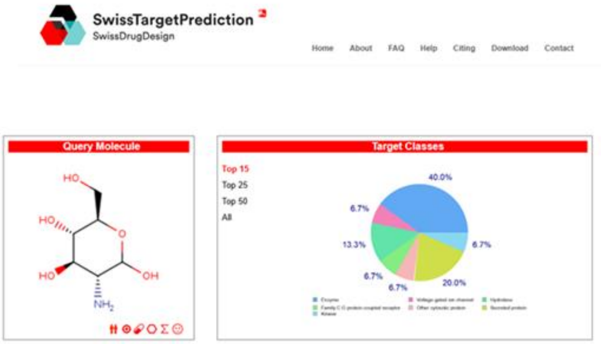

Figure 4: SwissADME was used to represent the query molecule and its target classes; including the top 15 targets for Modified Chitosan.

The top 15 targets for Modified Chitosan include 40% enzymes, 20% secreted protein, 13.3% family CG protein-coupled receptor, 6.7% voltage-gated ion channel, 6.7% other cytosolic proteins and 6.7% hydrolase.

The result for SwissADME analysis was as follow: Highly soluble in water, low gastrointestinal absorption. Not permeant across BBB (Blood Brain Barrier) so it cannot reach the brain and central nervous system and remained in the blood or body fluids. P-gp substrate stands for P-glycoprotein, a protein that acts as a "pump" in the body. It is found in many tissues, including the intestines, liver, kidneys, and the blood-brain barrier. If a compound is a P-gp substrate, it means that P-gp can actively transport (pump) the compound out of cells. This can affect the drug's absorption, distribution, and effectiveness. Do not inhibit CYP enzymes and do not interact with other drugs (no drug-drug interaction). Log Kp (the logarithmic value of the skin permeation coefficient): -9.88 cm/s. It is often used to predict a compound's lipophilicity (affinity for fats or oils) and its ability to cross biological membranes, such as the skin. A higher log K value indicates that the compound is more lipophilic (fat-soluble), while a lower value indicates it is more hydrophilic (water-soluble) (Table 2).

Table 2: SwissADME pharmacokinetics parameters prediction of chitosan; Water Solubility, GI absorption, BBB permeant, P-gp substrate, CYP inhibitor, Log Kp and synthesis accessibility.

Water Solubility (Log S (ESOL)	Highly soluble 3.74
Log S (Ali)	Highly soluble 7.84
Log S (SILICOS-IT)	Soluble 4.49
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log Kp (skin permeation)	-9.88 cm/s
Synthetic accessibility	3.94

Lipinski's Rule of Five; is a set of criteria used to predict the likelihood that a compound will be orally bioavailable (able to be absorbed and distributed in the body when taken orally). The rule is based on four key physicochemical properties:

- Molecular Weight (MW) $\leq$ 500 g/mol.
- Log P (lipophilicity) $\leq$ 5.
- Hydrogen Bond Donors $\leq$ 5 (-OH or -NH groups).
- Hydrogen Bond Acceptors $\leq$ 10 (nitrogen or oxygen atoms).

A compound that violates more than one of these rules is less likely to be orally bioavailable [42].

"Lipinski: yes" This means the compound follows Lipinski's Rule of Five, it meets the criteria for good oral bioavailability based on its physicochemical properties. Zero violation: This means the compound does not violate any of the four Lipinski rules. It fully complies with all the criteria, making it a strong candidate for further development as an orally administered drug.

Veber's Rules (Veber yes) are a set of guidelines used to predict the oral bioavailability of a compound. They focus on two key properties:

1. Rotatable Bonds: Should be $\leq$ 10. Rotatable bonds are single bonds that can freely rotate (e.g., bonds between carbon atoms or between carbon and heteroatoms like nitrogen or oxygen).
2. Topological Polar Surface Area (TPSA): Should be $\leq 140\ \text{Å}^2$. TPSA measures the surface area of a molecule that is polar (e.g., due to oxygen, nitrogen, or hydrogen atoms). It is related to a compound's ability to form hydrogen bonds and cross cell membranes. A compound that meets both criteria is considered to have good oral bioavailability [43].

"Egan yes": This means the compound fully complies with Egan's Rules.

"Muegge no": This means the compound does not fully comply with Muegge's Criteria.

Bioavailability Score 0.55: The Bioavailability Score is a value between 0 and 1 that predicts the likelihood of a compound being orally bioavailable. Oral bioavailability refers to the fraction of a drug that reaches the systemic circulation after oral administration. The score is determined by evaluating various physicochemical properties, such as Lipinski's Rule of Five, Veber's Rules, and Egan's Rules. PAINS (Pan-Assay Interference Compounds) refer to compounds that cause nonspecific interference with assay results, often resulting in false-positive results. These compounds often:

- React with assay components (proteins or reagents).
- Aggregate in solution.
- Fluoresce or absorb light in a way that interferes with detection.

"PAINS: zero alert": This means the compound does not contain any PAINS substructures.

Brenk Alerts: Brenk alerts are based on a set of rules developed by Christian Brenk and colleagues to identify problematic substructures in compounds. These substructures are often associated with:

- Toxicity.
- Poor pharmacokinetic properties.
- Chemical reactivity that can lead to instability or nonspecific interactions.

"Brenk: zero alert": This means the compound does not contain any problematic substructures identified by the Brenk rules [44].

Synthetic Accessibility (SA) Score: 3.94: The Synthetic Accessibility Score is a value that predicts how easily a compound can be synthesized in a laboratory. It is typically represented on a scale from 1 to 10, where:

- Score -1 means the compound is very easy to synthesize.
- Score -10 means the compound is very difficult to synthesize.

The score is calculated based on factors such as:

- Molecular complexity
- Availability of starting materials.
- Number of synthetic steps required.

"Consensus Log P a/w: -2.54"

A Log P of -2.54 indicates that the compound is highly hydrophilic (water-soluble) and has very low lipophilicity (Figure 5) (Table 3).

Table 3: SwissADME drug likeness parameters prediction of chitosan; Lipinski, Ghose, Veber, Egan, Muegge, Bioavailability Score, PAINS, Brenk and Consensus Log Po/w.

Table 3: SwissADME drug likeness parameters prediction of chitosan; Lipinski, Ghose, Veber, Egan, Muegge, Bioavailability Score, PAINS, Brenk and Consensus Log Po/w.

Lipinski	Yes; 0 violation
Ghose	No; 2 violations: WLOGP<-0.4, MR<40

Veber	Yes
Egan	Yes
Muegge	No; 2 violations: MW<200, XLOGP3<-2Yes
Bioavailability Score	0.55
PAINS	0 Alert
Brenk	0 Alert
Consensus Log Po/w	-2.54

Figure 5: SwissADME was used to represent the water solubility, pharmacokinetics, drug-likeness, medicinal chemistry, physiochemical properties and lipophilicity.

Discussion

The pervasive presence of microplastics in human body fluids has emerged as a critical environmental and public health challenge, demanding innovative solutions for their effective removal. In this study, we harness the potential of computational design to strategically modify chitosan a naturally occurring, biocompatible, and biodegradable polymer into a high-performance adsorbent for microplastics. Utilizing cutting-edge computational tools such as PubChem, Avogadro, PyMOL, and SwissADME.

Chitosan is already known for its affinity for plastics and its biocompatibility. It is a naturally derived polysaccharide with a high molecular weight of approximately 1526.5 g/mol (as obtained from PubChem), presents significant challenges for biomedical applications due to its limited solubility and poor absorption by human cells [45]. The SMILES code of chitosan, retrieved from PubChem, reveals its complex polymeric structure, which hinders its ability to dissolve effectively in body fluids and interact with biological systems. To address these limitations, we propose a strategic fragmentation of chitosan into smaller, low-molecular-weight fragments (Done by Avogadro) This approach aims to enhance its bioavailability, improve solubility, and facilitate cellular uptake, thereby unlocking its full potential as a functional biomaterial. By reducing the molecular weight, we anticipate not only improved pharmacokinetic properties but also a greater capacity for targeted interactions, such as the adsorption of microplastics or other contaminants in biological environments. This modification represents a critical step toward optimizing chitosan for advanced biomedical and environmental applications, bridging the gap between its inherent biocompatibility and practical utility in complex physiological systems. The four smaller fragments were visualized by PyMOL to check the 3D structure of each part.

SwissADME: Fragmented Chitosan is pH-dependent water soluble, more soluble in acidic environments. Higher water solubility would make it more effective in body fluids, with different pH levels. It also can stay and circulate longer in the body, increasing microplastics adsorption chances. It also can be excreted more easily reducing potential toxicity. Native chitosan's high molecular weight (e.g., ~1526.5 g/mol) and rigid polymeric structure (evident from its SMILES code) limit its solubility in neutral or physiological pH environments, strategic modifications such as fragmentation into lower molecular weight derivatives can significantly improve its hydrophilicity. This solubility offers two critical advantages:

- **Enhanced Dispersion and Bioavailability:** Soluble chitosan fragments can uniformly disperse in body fluids (blood, interstitial fluid), maximizing their surface area and accessibility to microplastics. This ensures efficient contact between chitosan's functional groups (amine -NH_2 and hydroxyl -OH) and microplastic surfaces, enabling stronger adsorption via hydrogen bonding, electrostatic interactions, or hydrophobic forces.

- **Improved Biocompatibility and Safety:** Water-soluble chitosan derivatives are less likely to aggregate in tissues or organs, reducing the risk of unintended inflammation or toxicity. Their solubility also facilitates renal clearance post-adsorption, ensuring that chitosan-microplastic complexes can be safely excreted from the body without long-term retention.

No CYP enzymes inhibitors; No drug-drug interactions (DDIs).

Selective Adsorption of Microplastics: Chitosan's adsorption mechanism primarily relies on physical interactions (e.g., hydrogen bonding, electrostatic forces, and hydrophobic interactions) with microplastics rather than chemical reactions with other molecules. This selectivity ensures that chitosan targets microplastics specifically, without binding to or altering the function of drugs, proteins, or other biomolecules in the body. Reduced Risk of Systemic Toxicity: Unlike some synthetic adsorbents or chelating agents, chitosan is biocompatible and biodegradable, with a well-established safety profile. Its lack of DDIs further minimizes the risk of systemic toxicity, making it suitable for long-term or repeated use in microplastic removal applications. Ease of Regulatory Approval: The absence of DDIs simplifies the regulatory pathway for chitosan-based adsorbents, as it reduces the complexity of safety assessments.

Log Kp : -9.88 cm/s: Skin permeation refers to the ability of a compound to pass through the skin. This is an important property for drugs designed for transdermal delivery such as patches or creams. The value -9.88 cm/s is the logarithmic value of the skin permeation coefficient (log Kp). A more negative value (-9.88 cm/s) means the compound has very low skin permeation and is unlikely to pass through the skin effectively. A less negative value (closer to 0) means the compound has higher skin permeation and can more easily cross the skin barrier.

Such a compound would likely not be suitable for transdermal drug, oral administration is the best rout.

Lipinski yes: If SwissADME gives a result of "Lipinski yes" and "0 violation", it means the compound is highly likely to have good oral bioavailability and is considered a promising candidate for drug development.

"Veber yes": This means the compound fully complies with Veber's Rules. In other words:

- It has ≤ 10 rotatable bonds.
- It has a TPSA ≤ 140 Å².

Such a compound is considered to have good oral bioavailability and is more likely to be successfully developed as an oral drug.

"Egan yes":

- This means the compound fully complies with Egan's Rules. In other words:
- It has a TPSA ≤ 131.6 Å².
- It has a Log P ≤ 5.88.

Such a compound is considered to have good oral bioavailability and is more likely to be successfully developed as an oral drug.

Muegge no": This means the compound does not fully comply with Muegge's Criteria. In other words, it violates one or more of the rules, making it less likely to be drug-like. "MW < 200": This means the compound has a molecular weight (MW) of less than 200 g/mol. According to Muegge's Criteria, the molecular weight should be between 200 and 600 g/mol. A compound with MW < 200 is too small and may lack the necessary complexity to interact effectively with biological targets." XLOGP3 < -2": XLOGP3 is a calculated measure of lipophilicity (how well a compound dissolves in fats/oils). The value < -2 means the compound is very hydrophilic (water-soluble).

Bioavailability Score 0.55: The score is calculated based on a combination of physicochemical properties, including: Lipinski's Rule of Five, Veber's Rules and Egan's Rules. A higher score indicates a higher likelihood of good oral bioavailability. A score of 0.55 means the compound has a moderate likelihood of being orally bioavailable. This score is a useful early indicator but should be validated with experimental data (in vitro or in vivo). Among the candidate compounds, chitosan shows a relatively high bioavailability score of approximately 0.55, making it a promising option for microplastic adsorption. β-cyclodextrin follows closely with a score around 0.5, while other biopolymers such as zein (~0.5), polydopamine (~0.4), alginate (~0.3), and cellulose nanofibers (~0.2–0.4) demonstrate lower predicted bioavailability. Activated carbon, although effective for adsorption, is not biodegradable or bioavailable, making it less suitable for biomedical or biocompatible applications [46,47]

"PAINS: zero alert": This means the compound does not contain any PAINS substructures. In other words, it is not flagged as a pan-assay interference compound. A compound with zero PAINS alerts is less likely to interfere with biological assays and less likely to produce false-positive results in biological assays and is considered more reliable for further testing.

"Brenk: zero alert": This means the compound does not contain any problematic substructures identified by the Brenk rules. In other words, it is not flagged for having any known toxic or reactive groups. A compound with zero Brenk alerts is considered less likely to have toxicity or stability issues and is more suitable for further development.

Synthetic Accessibility (SA) Score: 3.94:

A score of 3.94 means the compound is relatively easy to synthesize. It falls on the lower end of the scale, indicating that:

- The compound has low to moderate molecular complexity.
- The required starting materials are likely readily available.
- The synthesis process is likely straightforward and feasible.

"Consensus Log P a/w: -2.54"

A Log P of -2.54 indicates that the compound is highly hydrophilic (water-soluble) and has very low lipophilicity. This means:

- Is very water-soluble and may have poor membrane permeability.
- Could be suitable for targets in aqueous environments (extracellular targets).

4. Conclusions

Modification chitosan into low-molecular-weight, water-soluble derivatives offers a promising approach that warrants further investigation to microplastic contamination in the human body. Modified chitosan, with its biocompatibility, biodegradability, and lack of drug interactions, serves as a safe and effective oral adsorbent that selectively binds microplastics in the gastrointestinal tract. Through advanced computational design and molecular engineering (Avogadro, PyMOL and SWISSADME) its properties are optimized for efficient adsorption without disrupting physiological processes or medications. As a natural, sustainable, and non-toxic material, chitosan aligns with the demand for eco-friendly health solutions. This innovation highlights the integration of molecular and environmental sciences, positioning chitosan as a promising functional food supplement to address microplastic exposure and advance biomaterial design for public health challenges.

DECLARATIONS

1- Authors' contributions (CRediT Taxonomy)

Contributor Role	Degree of Contribution		
	Lead	Equal	Supporting
Conceptualization	KAS		ZAS
Data curation	KAS		ZAS
Formal analysis	KAS		ZAS
Funding acquisition	ZAS		KAS
Investigation	ZAS		KAS
Methodology	ZAS		KAS
Project administration	KAS		ZAS
Resources	KAS		ZAS
Software	KAS		ZAS
Supervision	KAS		ZAS
Validation	ZAS		KAS
Visualization	ZAS		KAS
Writing-original draft	KAS		ZAS
Writing-review & editing	ZAS		KAS

2- **-Ethical approval:** The study was approved by the relevant ethics committee. Informed consent was obtained from all participants.

3- **-Funding resources:** No funding resources.

4- **-Conflict of interest:** The authors declare no conflict of interest with other previous studies.

References

[1] Haripriya S, Vijayalakshmi M, Ala C, Murugesan S, Pavadai P, Kunjiappan S, Pandian SR. Pharmacoinformatics-based prediction of Checkpoint kinase-1 inhibitors from Momordica charantia Linn. for cancer. Computational Biology and Chemistry. 2025 Apr 1;115:108286https://doi.org/10.1016/j.compbiolchem.2025.108286.

[2] Karami-Gadallo L, Ataie-Fashtami L, Ghoranneviss M, Pouladian M, Sardari D. Cell damaging by irradiating non-thermal plasma to the water: Mathematical modeling of chemical processes. Molecular Biology Research Communications. 2018 Sep;7(3):133https://doi.org/10.22099/mbrc.2018.28869.1233.

[3] Wei C, Zhang H, Niu L, Zhong Q, Yan H, Wang J. 4D-QSAR, ADMET properties, and molecular dynamics simulations for designing N-substituted urea/thioureas as human glutaminyl cyclase inhibitors. Computational Biology and Chemistry. 2024 Oct 1;112:108131https://doi.org/10.1016/j.compbiolchem.2024.108131.

[4] Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: the trinity at the heart of the DNA damage response. Molecular cell. 2017 Jun 15;66(6):801-17https://doi.org/10.1016/j.molcel.2017.05.015.

[5] Reisländer T, Groelly FJ, Tarsounas M. DNA damage and cancer immunotherapy: a STING in the tale. Molecular cell. 2020 Oct 1;80(1):21-8https://doi.org/10.1016/j.molcel.2020.08.020.

[6] Galluzzi L, Yamazaki T, Kroemer G. Linking cellular stress responses to systemic homeostasis. Nature Reviews Molecular Cell Biology. 2018 Nov;19(11):731-45https://doi.org/10.1038/s41580-018-0058-6.

[7] Klapp V, Álvarez-Abril B, Leuzzi G, Kroemer G, Ciccia A, Galluzzi L. The DNA damage response and inflammation in cancer. Cancer discovery. 2023 Jul 7;13(7):1521-45https://doi.org/10.1158/2159-8290.CD-23-0213.

[8] Boekelheide K, Blumberg B, Chapin RE, Cote I, Graziano JH, Janesick A, Lane R, Lillycrop K, Myatt L, States JC, Thayer KA. Predicting later-life outcomes of early-life exposures. Environmental health perspectives. 2012 Oct;120(10):1353-61https://doi.org/10.1289/ehp.1104621.

[9] Kundakovic M, Jaric I. The epigenetic link between prenatal adverse environments and neurodevelopmental disorders. Genes. 2017 Mar 18;8(3):104https://doi.org/10.3390/genes8030104.

[10] Kheirabadi M, Maleki J, Soufian S, Hosseini S. Design of new potent HTLV-1 protease inhibitors: in silico study. Molecular Biology Research Communications. 2016 Mar;5(1):19https://doi.org/10.22099/mbrc.2016.2929.

[11] Javanmard A, Azimzadeh-Irani M, Tafazzoli G, Esmaeilzadeh A, Shirinpoor-Kharf M, Haghayeghi SM. In-silico structural analysis of Heterocephalus glaber amyloid beta: an anti-Alzheimer's peptide. Molecular Biology Research Communications. 2024;13(1):29https://doi.org/10.22099/mbrc.2024.4550.

[12] Yang Y, Jalalah M, Alsareii SA, Harraz FA, Thakur N, Zheng Y, Koutb M, Yoon Y, Salama ES. Plastic waste and microplastics (MPs) formation: Management, migration, and environmental

impact. Journal of Environmental Chemical Engineering. 2024 May 4:112926 DOI: 10.1016/j.jece.2024.112926.

[13] Hartmann NB, Huffer T, Thompson RC, Hassellov M, Verschoor A, Daugaard AE, Rist S, Karlsson T, Brennholt N, Cole M, Herrling MP. Are we speaking the same language? Recommendations for a definition and categorization framework for plastic debris. 2019; 53(3), 1039–1047 https://doi.org/10.1016/j.envpol.2019.03.013.

[14] Yee MS, Hii LW, Looi CK, Lim WM, Wong SF, Kok YY, Tan BK, Wong CY, Leong CO. Impact of microplastics and nanoplastics on human health. Nanomaterials. 2021 Feb 16;11(2):496 https://doi.org/10.3390/nano11020496.

[15] Li D, Shi Y, Yang L, Xiao L, Kehoe DK, Gun'ko YK, Boland JJ, Wang JJ. Microplastic release from the degradation of polypropylene feeding bottles during infant formula preparation. Nature Food. 2020 Nov;1(11):746-54 https://doi.org/10.1038/s41574-020-00326-2.

[16] Li S, Keenan JI, Shaw IC, Frizelle FA. Could microplastics be a driver for early onset colorectal cancer?. Cancers. 2023 Jun 24;15(13):3323 https://doi.org/10.3390/cancers15133323.

[17] Qiao R, Sheng C, Lu Y, Zhang Y, Ren H, Lemos B. Microplastics induce intestinal inflammation, oxidative stress, and disorders of metabolome and microbiome in zebrafish. Science of the Total Environment. 2019 Apr 20;662:246-53 DOI: 10.1016/j.scitotenv.2019.01.245.

[18] Roshid A, Abbas K, Aziz IH. Polymorphism Of Angiotensin Converting Enzymegene In A Sample of Iraqi Hypertensive Patient and Its Association with Body Mass Index. Biochemical & Cellular Archives. 2019 Apr 1;19(1) https://doi.org/10.35080/bca.v19i1.1206.

[19] Im J, Eom HJ, Choi J. Effect of early-life exposure of polystyrene microplastics on behavior and DNA methylation in later life stage of zebrafish. Archives of Environmental Contamination and Toxicology. 2022 May;82(4):558-68 DOI: 10.1007/s00244-022-00924-9.

[20] Fadare OO, Wan B, Guo LH, Zhao L. Microplastics from consumer plastic food containers: are we consuming it?. Chemosphere. 2020 Aug 1;253:126787 10.1016/j.chemosphere.2020.126787.

[21] Ahmed MB, Rahman MS, Alom J, Hasan MS, Johir MA, Mondal MI, Lee DY, Park J, Zhou JL, Yoon MH. Microplastic particles in the aquatic environment: A systematic review. Science of the Total Environment. 2021 Jun 25;775:145793 https://doi.org/10.1016/j.scitotenv.2021.145793.

[22] Mohamed Nor NH, Koelmans AA. Transfer of PCBs from microplastics under simulated gut fluid conditions is biphasic and reversible. Environmental science & technology. 2019 Jan 14;53(4):1874-83 https://doi.org/10.1021/acs.est.8b06288.

[23] Segovia-Mendoza M, de León CT, García-Becerra R, Ambrosio J, Nava-Castro KE, Morales-Montor J. The chemical environmental pollutants BPA and BPS induce alterations of the proteomic profile of different phenotypes of human breast cancer cells: A proposed interactome. Environmental Research. 2020 Dec 1;191:109960 https://doi.org/10.1016/j.envres.2020.109960.

[24] Yin K, Wang Y, Zhao H, Wang D, Guo M, Mu M, Liu Y, Nie X, Li B, Li J, Xing M. A comparative review of microplastics and nanoplastics: Toxicity hazards on digestive, reproductive and nervous system. Science of the total environment. 2021 Jun 20;774:145758 https://doi.org/10.1016/j.scitotenv.2021.145758.

[25] Campanale C, Massarelli C, Savino I, Locaputo V, Uricchio VF. A detailed review study on potential effects of microplastics and additives of concern on human health. International journal of environmental research and public health. 2020 Feb;17(4):1212 https://doi.org/10.3390/ijerph17041212.

[26] Zhao K, Wei Y, Dong J, Zhao P, Wang Y, Pan X, Wang J. Separation and characterization of microplastic and nanoplastic particles in marine environment. Environmental Pollution. 2022 Mar 15;297:118773 https://doi.org/10.1016/j.envpol.2021.118773.

[27] Smith M, Love DC, Rochman CM, Neff RA. Microplastics in seafood and the implications for human health. Current environmental health reports. 2018 Sep;5:375-86 https://doi.org/10.1007/s40572-018-0206-1.

[28] Sharma S, Sharma B, Sadhu SD. Microplastic profusion in food and drinking water: are microplastics becoming a macroproblem?. Environmental Science: Processes & Impacts. 2022;24(7):992-1009 https://doi.org/10.1039/d2em00072a.

[29] Sahan KA, Aziz IH, Dawood SN, Al Qazzaz H. The role of resistin gene polymorphism in Iraqi breast cancer patients. Biomedicine. 2022 Dec 31;42(6):1296-300https://doi.org/10.38013/biomedicine.42.6.1296-1300.

[30] Potischman N, Troisi R. In-utero and early life exposures in relation to risk of breast cancer. Cancer Causes & Control. 1999 Dec;10:561-73 https://doi.org/10.1023/A:1008891105171.

[31] Ma L, Yu H, Wang X, Li D, Zhang Y, Pei X, Duan Z, Ma M. The effects of maternal exposure to BPA during pregnancy on the male reproductive system and the testicular microRNA expression profile. Environmental Science and Pollution Research. 2020 May;27:17290-302.

[32] Rai N, Kailashiya V, Gautam V. Exploring the protective effect against 7, 12-dimethylbenz [a] anthracene-induced breast tumors of

palmitoylethanolamide. ACS Pharmacology & Translational Science. 2023 Dec 1;7(1):97-109.

[33] Sahan, K. A., Aziz, I. H., Dawood, S. N., & Abdul Razzaq, S. S. (2023). The effect of genetic polymorphism of resistin gene among iraqi breast cancer women. Iraqi journal of biotechnology, 22(1), 1-7.

[34] Segovia-Mendoza M, Nava-Castro KE, Palacios-Arreola MI, Garay-Canales C, Morales-Montor J. How microplastic components influence the immune system and impact on children health: Focus on cancer. Birth defects research. 2020 Oct;112(17):1341-61.

[35] Xia L, Gu W, Zhang M, Chang YN, Chen K, Bai X, Yu L, Li J, Li S, Xing G. Endocytosed nanoparticles hold endosomes and stimulate binucleated cells formation. Particle and fibre toxicology. 2016 Dec;13:1-2.

[36] Prata JC, Da Costa JP, Lopes I, Duarte AC, Rocha-Santos T. Environmental exposure to microplastics: An overview on possible human health effects. Science of the total environment. 2020 Feb 1;702:134455.

[37] Chatterjee S, Sharma S. Microplastics in our oceans and marine health. Field Actions Science Reports. The Journal of Field Actions. 2019 Mar 1(Special Issue 19):54-61.

[38] Kim H, Zaheer J, Choi EJ, Kim JS. Enhanced ASGR2 by microplastic exposure leads to resistance to therapy in gastric cancer. Theranostics. 2022 Apr 4;12(7):3217.

[39] Wang Y, Xu X, Jiang G. Microplastics exposure promotes the proliferation of skin cancer cells but inhibits the growth of normal skin cells by regulating the inflammatory process. Ecotoxicology and Environmental Safety. 2023 Nov 15;267:115636.

[40] Abdulhameed AS, Al Omari RH, Althahban S, Jazaa Y, Abualhaija M, Algburi S. Green vegetable waste composited with chitosan as a bioadsorbent for effective removal of methylene blue dye from water: Insight into physicochemical and adsorption characteristics. Biomass and Bioenergy. 2025 Feb 1; 193:10752810.20517/wecn.2024.09 .

[41] Biswas UK, Bose A, Ghosh B, Sharma S. An insight into chemically modified chitosan and their biological, pharmaceutical, and medical applications: A review. International Journal of Biological Macromolecules. 2025 Feb 3:140612.

[42] Singh R, Singh K. Lipinski s Rule of Five. In2-Deoxy-D-Glucose: Chemistry and Biology 2024 Nov 15 (pp. 242-246). Bentham Science Publishers.

[43] Mostafa MA, Ibrahim MA, Badran AS. Spectroscopic elucidation, quantum chemical computations (FMO, HOMO–LUMO, MEP, NLO), and biological activity on some novel heterocyclic compounds using 3-substituted-6, 8-dimethylchromones. Synthetic Communications. 2024 Sep 16;54(18):1523-50.

[44] Gupta S, Vasanth D, Kumar A. Physicochemical analysis of chitosan oligosaccharide revealed its usefulness in effective delivery of drugs. Journal of Biomaterials Science, Polymer Edition. 2025 Jan 2;36(1):45-63.

[45] Marianti A, Amalina ND, Mursiti S, Sitompul FN, Futri SS, Negara LG, Sholehah IK, Asmorowati DS, Astari PD. Pharmacokinetics Profile of Chitosan Nanoparticles in Chronic Lead-induced Toxicity Rats Model. Biosaintifika: Journal of Biology & Biology Education. 2024 Apr 20;15(1).

[46] Nicolaescu OE, Belu I, Mocanu AG, Manda VC, Rău G, Pîrvu AS, Ionescu C, Ciulu-Costinescu F, Popescu M, Ciocîlteu MV. Cyclodextrins: Enhancing Drug Delivery, Solubility and Bioavailability for Modern Therapeutics. Pharmaceutics. 2025 Feb 22;17(3):288.

[47] Kong C, Wang K, Sun L, Zhao H, Wang T, Zhou W, Wu D, Xu F. Novel carbon dots derived from moutan cortex significantly improve the solubility and bioavailability of mangiferin. International Journal of Nanomedicine. 2024 Dec 31:3611-22.